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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/386,709	08/31/1999	DAVID J. BRAYDEN	99.1081.US	1709

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ELAN HOLDINGS INC
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EXAMINER
GRASER, JENNIFER E

ART UNIT	PAPER NUMBER
1645	18

DATE MAILED: 04/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/386,709	Brayden
Examiner	**Art Unit**
Jennifer Graser	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Amendment 17B, 2/28/02* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *21-25, 27-31, 33, and 35-37* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *21-25, 27-31, 33, and 35-37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted 2/28/02, Paper No. 17B is made. Claims 21-25, 27-31, 33 and 35-37 are currently pending.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 21-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Shahin (Infect. Immun. 1995. 63(4): 1195-1200).

Jones et al teach that fimbriae from *Bordetella pertussis* encapsulated in poly(lactide-co-glycolide) microparticles of a size appropriate for uptake by the immune inductive tissues of the gastrointestinal tract could *protect* mice from *B.pertussis* respiratory infection upon oral administration (abstract). It is disclosed that the mean diameter of the microparticles was 2.04um, i.e., less than 3um, with 90% of microparticles having diameters within the narrow range of 0.8 to 5.3 um (see page 490, Results section). The microparticles were prepared through a solvent extraction technique (top of page 490, column 1). It is further disclosed that analysis of

the mechanism of particle uptake by M cells in mouse gut has clearly shown that this is restricted to materials with diameters less than or equal to 10um (page 492, column 2). It is further disclosed that smaller microparticles (1- to 10- um) were more immunogenic than larger particles (20- to 50- um), as the smaller microparticles were rapidly phagocytosed and distributed (page 290, column 1).

However, Jones et al does not particularly exemplify the use of at least a first and second subpopulation of microparticles wherein each subpopulation comprises different antigens.

Shanin et al disclose that purified *Bordetella pertussis* antigens, encapsulated in biodegradable poly (DL-lactide-cp-glycolide) (DL-PLG) microspheres are effective vaccines. The reference discloses that microencapsulated pertussis toxoid, filamentous hemagglutinin, and pertactin all retained their immunogenicity when administered parenterally (abstract). It is also disclosed that intranasal administration of these microencapsulated antigens elicited high levels of specific antibody coinciding with protection against infection when these microspheres are administered to the respiratory tract, i.e., a TH2-polarized protective immune response (abstract). Shanin specifically discloses that intranasal administration of a combination of 1ug each of *each* of the microencapsulated B.pertussis antigens (i.e, microencapsulated pertussis toxoid; microencapsulated filamentous hemagglutinin; and microencapsulated pertactin) was more effective in reducing bacterial infection than administration of any single microencapsulated antigen. See abstract. This teaches that subpopulations of different microencapsulated antigens from *B.pertussis* allow for a better immune response than a single microencapsulated population.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include one or more subpopulations of different microencapsulated *B.pertussis* antigens when orally administering the microencapsulated population of *B.pertussis* fimbriae taught by Jones et al. because Shahin specifically teaches that the administration of different populations of microencapsulated *B.pertussis* antigens (also encapsulated in poly(lactide-co-glycolide) more effectively reduce bacterial infection than any single microencapsulated *B.pertussis* antigen. Further, one of ordinary skill in the art would have been motivated to administer these subpopulations of microparticles by the *oral route* as taught by Jones et al. because Jones et al specifically teach that no evidence for the elicitation of a disseminated mucosal response following intranasal administration with *B.pertussis* antigens (as taught by Shahin) has been seen, suggesting that this route of administration may not be appropriate for inducing immunity against all pathogens and that immunization of mucosae at one of the components of the common mucosal immune system may be a prerequisite for the induction of extended secretory responses (see page 491, column 2). Further, Jones et al teach that in all studies of administering acellular pertussis vaccines orally, either as free antigen or microencapsulated, stimulation of both local mucosal immunity and serum immunoglobulins, i.e., TH2 polarized immune response, was seen and resulted in protection of the host against challenge with live *B.pertussis*. Jones specifically sets forth the appropriate size range for such oral administration; therefore, it would have been obvious to one of ordinary skill in the art to produce microparticles comprising pertussis toxoid, filamentous hemagglutinin or pertactin of

such size and to administer them orally since, Jones et al points out that the oral administration route appears to be critical for achieving immune protection which was not achieved through the intranasal route in Shahin.

3. Claims 28-31, 33 and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Shahin (Infect. Immun. 1995. 63(4): 1195-1200) as applied to claims 21-25 and 27 above, and further in view of Singh et al (Vaccine, 1998, 16(4): 346-352) or O'Hagan et al (US 5,603,960).

The combined teachings of Jones and Shahin are set forth above. Both references, as stated above, teach that a protective Th2 (humoral/antibody) type response was seen. However, they do not particularly exemplify that the microcapsules are nanoparticles wherein at least 50% are less than 600nm.

Singh et al disclose that diphtheria toxoid was encapsulated in microparticles prepared from polylactide-co-glycolide (PLG) polymers using a solvent evaporation technique (abstract). It is disclosed that rats were immunized with PLG microparticles containing the diphtheria toxoid with all microparticles being less than 10um. Another group of mice were given microparticles of greater than 10um. See page 348, column 1. It is disclosed that the "mean size for the smaller microparticles was about **500nm**, the ideal size for phagocytosis by antigen presenting cells" (see page 350, column 2). It is disclose that while two antigens in the *same* microparticle had a less potent antibody response than a single encapsulated antigen, this appears to be due to antigenic competition between the two antigens within the **same** microparticle.

However, Singh does specifically recite that two or more batches of microparticles with different rates of antigen may be prepared and combined to provide a single dose vaccine (page 347). These teachings do not suggest that two different antigens encapsulated in two different microparticles would suffer from this same antigenic competition. In fact, Shanin specifically discloses that intranasal administration of a combination of 1ug each of *each* of the microencapsulated B.pertussis antigens (i.e, microencapsulated pertussis toxoid; microencapsulated filamentous hemagglutinin; and microencapsulated pertactin) was more effective in reducing bacterial infection than administration of any single microencapsulated antigen

O'Hagan et al describe methods for producing microparticles useful in the formulation of pharmaceutical compositions. Methods of immunizing mammals against diseases comprising administering to the mammal an effective amount of antigen-containing microparticles. Vaccines comprising a pharmaceutical composition comprising said microparticles are also disclosed. It is disclosed that the preferred average microparticle size is between 200 nm and 200um (column 3, lines 33-34). It is disclosed that when the microparticles are to be orally administered, the preferred size of the microparticles is preferably between 100 nanometers to 10 um in size (column 7, lines 21-23). It is preferred that the microparticles be administered orally (column 3, lines 40-41). It is disclosed that the microparticles are preferably made with a biodegradable polymer (column 4, lines 63-3). The solvent media used in the solvent evaporation method to produce the microparticles is dependent upon the material to be

encapsulated (column 4, lines 60-63). The preferred polymer for encapsulating the bioactive material is a polylactide polymer, or particularly a polylactide-co-glycolide polymer (column 5, lines 24-30).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use nanoparticles less than 600nm as taught by O'Hagan and Singh, or microparticles less than 5um as taught by Jones, because the prior art specifically discloses that particle uptake by M cells in the mouse gut is restricted to materials with diameters less than or equal to 10um (page 492, column 2) and that smaller microparticles (1- to 10- um) were more immunogenic than larger particles (20- to 50- um), as the smaller microparticles were rapidly phagocytosed and distributed (page 290, column 1). O'Hagan teaches vaccine compositions comprising microparticles of 100nm to 10 um in size which are made of the same polymers as those used in the methods of Shanin and Jones and uses similar methods to produce the microparticles. Singh et al specifically discloses that the "mean size for the smaller microparticles was about **500nm**, the ideal size for phagocytosis by antigen presenting cells" (see page 350, column 2). Since Jones and Shahin, also teach DL-PLG encapsulated antigen as vaccines, and specifically teach that the use of smaller microparticles allows for a more rapid phagocytosis and distribution, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make the particles less than 500 or 600nm, absent unexpected or unobvious results, because a person of ordinary skill in the art would expect such a microparticle to improve the immune response of the method. One of ordinary skill in the art would have a

wide knowledge of the appropriate size to make the microparticles depending on their objectives given the large amount of literature available in the prior art at the time the invention was made.

4. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Shahin (Infect. Immun. 1995. 63(4): 1195-1200) as applied to claims 21-25 and 27 above, and further in view of Andrianov (US Patent No. 5,807,757).

The teachings of Jones and Shahin are set forth above. However, they do not particularly teach that the microparticles were formed by coacervation.

Andrianov et al disclose a method for preparing polyphosphazene microspheres by coacervation (abstract). Andrianov et al disclose that the process of coacervation allows for the microspheres to be produced with a controlled microsphere size distribution without the use of elevated temperatures, organic solvents, water-insoluble core materials or complex manufacturing equipment, such as spray equipment and eliminates generation of the aerosol (column 2, lines 15-23 and lines 51-55). It is taught that the coacervation process is highly reproducible and generates microspheres with an improved, more narrow microsphere size distribution compared to the spray technique and, contrary to the microspheres obtained by spray method, coacervation microspheres do not contain significant amount of larger size aggregates or amorphous precipitate (column 2, lines 55-60). It is specifically taught that this important for the preparation of microspheres for vaccine delivery since the uptakes of these microspheres by M cells is limited to the particles having a diameter of 10um or less (column 2, lines 61-65). It is

disclosed that biological material can be encapsulated by mixing the material with either polyphosphazene solution before microsphere preparation, or with prepared polyphosphazene microspheres (col. 2, lines 24-29). Andrianov et al teach that the phosphazene polyelectrolyte is preferably *biodegradable* to prevent eventual deposition and accumulation of polymer molecules at distant sites in the body, such as the spleen (column 4, lines 32-40). The paragraph bridging columns 5 and 6, disclose that the microspheres formed by coacervation, may be employed as carriers of a biological material such as an antigen, which is capable of eliciting an immune response in an animal. The antigen may be derived from a cell, bacterium, virus particle or a portion thereof and may be a protein, peptide, polysaccharide, glycoprotein, glycolipid, nucleic acid, or combination thereof which elicits an immune response in an animal, including mammals, birds and fish (column 6,lines 1-10). It is taught that the microspheres which contain antigen may be administered as a vaccine by any method known to those skilled in the art that elicits an immune response, including parenterally, orally or by transmembrane or transmucosal administration (column 6, lines 30-40). The use of pharmaceutically acceptable carrier with the microspheres, i.e., PBS, is taught. It is taught that coacervation enables one to recover an increased yield of microspheres having a size in the micron range (up to 90 differential percent by volume and 95 differential percent by number), and produce microspheres of other sizes if needed without the use of elaborate equipment (column 5, lines 55-61). Example 9 teaches that 90% of particles by number and size are smaller than 6.6um, Example 6 teaches that

microparticles with a mean size between 4-6um were formed and Example 2 teaches that the percentage of microspheres under 10um is 90%(by volume) and 99.7% (by number).

It would have been prima facie obvious to one of ordinary skill in the art to produce the microparticles taught by Jones and Shahin by the coacervation methods taught by Andrianov et al because the primary references teach that PLG are biodegradable polymers with a long history of safe use in humans and Andrianov specifically teach that coacervation methods have many advantages over solvent evaporation methods, such as highly reproducible and generates microspheres with an improved, more narrow microsphere size distribution compared to the spray technique and, contrary to the microspheres obtained by spray method, coacervation microspheres do not contain significant amount of larger size aggregates or amorphous precipitate (column 2, lines 55-60). Absent evidence to the contrary, one of ordinary skill in the art would expect another biodegradable polymer, such as PLG, to work equally as well in the coacervation methods taught by Andrianov et al. and would allow for the production of a safe and effective microparticle vaccine.

5. Claims 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Infect.Immun., 1996, 64(2): 489-494) in view of Shahin (Infect. Immun. 1995. 63(4): 1195-1200) in view of Singh et al (Vaccine, 1998, 16(4): 346-352) or O'Hagan et al (US 5,603,960) as applied to claims 28-31, 33 and 35-37 above, and further in view of Andrianov.

The combination of primary references do not particularly teach that the microparticles were formed by coacervation.

Andrianov et al disclose a method for preparing polyphosphazene microspheres by coacervation (abstract). Andrianov et al disclose that the process of coacervation allows for the microspheres to be produced with a controlled microsphere size distribution without the use of elevated temperatures, organic solvents, water-insoluble core materials or complex manufacturing equipment, such as spray equipment and eliminates generation of the aerosol (column 2, lines 15-23 and lines 51-55). It is taught that the coacervation process is highly reproducible and generates microspheres with an improved, more narrow microsphere size distribution compared to the spray technique and, contrary to the microspheres obtained by spray method, coacervation microspheres do not contain significant amount of larger size aggregates or amorphous precipitate (column 2, lines 55-60). It is specifically taught that this important for the preparation of microspheres for vaccine delivery since the uptakes of these microspheres by M cells is limited to the particles having a diameter of 10um or less (column 2, lines 61-65). It is disclosed that biological material can be encapsulated by mixing the material with either polyphosphazene solution before microsphere preparation, or with prepared polyphosphazene microspheres (col. 2, lines 24-29). Andrianov et al teach that the phosphazene polyelectrolyte is preferably *biodegradable* to prevent eventual deposition and accumulation of polymer molecules at distant sites in the body, such as the spleen (column 4, lines 32-40). The paragraph bridging columns 5 and 6, disclose that the microspheres formed by coacervation, may be employed as carriers of a biological material such as an antigen, which is capable of eliciting an immune response in an animal. The antigen may be derived from a cell, bacterium, virus particle or a

portion thereof and may be a protein, peptide, polysaccharide, glycoprotein, glycolipid, nucleic acid, or combination thereof which elicits an immune response in an animal, including mammals, birds and fish (column 6,lines 1-10). It is taught that the microspheres which contain antigen may be administered as a vaccine by any method known to those skilled in the art that elicits an immune response, including parenterally, orally or by transmembrane or transmucosal administration (column 6, lines 30-40). The use of pharmaceutically acceptable carrier with the microspheres, i.e., PBS, is taught. It is taught that coacervation enables one to recover an increased yield of microspheres having a size in the micron range (up to 90 differential percent by volume and 95 differential percent by number), and produce microspheres of other sizes if needed without the use of elaborate equipment (column 5, lines 55-61). Example 9 teaches that 90% of particles by number and size are smaller than 6.6um, Example 6 teaches that microparticles with a mean size between 4-6um were formed and Example 2 teaches that the percentage of microspheres under 10um is 90%(by volume) and 99.7% (by number).

It would have been prima facie obvious to one of ordinary skill in the art to produce the microparticles taught the primary references by the coacervation methods taught by Andrianov et al because the primary references teach that PLG are biodegradable polymers with a long history of safe use in humans and Andrianov specifically teach that coacervation methods have many advantages over solvent evaporation methods, such as highly reproducible and generates microspheres with an improved, more narrow microsphere size distribution compared to the spray technique and, contrary to the microspheres obtained by spray method, coacervation

microspheres do not contain significant amount of larger size aggregates or amorphous precipitate (column 2, lines 55-60). Absent evidence to the contrary, one of ordinary skill in the art would expect another biodegradable polymer, such as PLG, to work equally as well in the coacervation methods taught by Andrianov et al. and would allow for the production of a safe and effective microparticle vaccine.

Response to Applicants' Arguments:

6. Applicants' arguments are rendered moot due to the substantive amendment to the claims which necessitated the new grounds of rejections. The arguments presented on pages 6-8 of the amendment were addressed in the new rejections set forth above. Briefly, Applicants argue that Singh et al teaches that two antigens in the same microparticle did not produce a good immune response, perhaps due to antigenic competition within the microcapsule. This has been fully and carefully considered but is not commensurate in scope with the claimed invention. The instant claims do not recite that two different antigens are encapsulated in the same microparticle. Additionally, Singh does not suggest that two different antigens encapsulated in two different microparticles would suffer from this same antigenic competition. Singh et al disclose that while two antigens in the *same* microparticle had a less potent antibody response than a single encapsulated antigen, this appears to be due to antigenic competition between the two antigens within the **same** microparticle. Further, Singh specifically recites that two or more batches of microparticles with different rates of antigen may be prepared and combined to provide a single dose vaccine (page 347). In fact, Shanin specifically discloses that intranasal administration of a

combination of 1ug each of *each* of the microencapsulated B.pertussis antigens (i.e, microencapsulated pertussis toxoid; microencapsulated filamentous hemagglutinin; and microencapsulated pertactin) was more effective in reducing bacterial infection than administration of any single microencapsulated antigen and Jones teaches that the reason Shanin did not achieve complete immune protection is not due to antigenic competition, but more likely due to the fact that these microcapsules were administered intranasally and not orally. Jones et al specifically teach that no evidence for the elicitation of a disseminated mucosal response following intranasal administration with *B.pertussis* antigens (as taught by Shahin) has been seen, suggesting that this route of administration may not be appropriate for inducing immunity against all pathogens and that immunization of mucosae at one of the components of the common mucosal immune system may be a prerequisite for the induction of extended secretory responses (see page 491, column 2). Further, Jones et al teach that in all studies of administering acellular pertussis vaccines orally, either as free antigen or microencapsulated, stimulation of both local mucosal immunity and serum immunoglobulins, i.e., TH2 polarized immune response, was seen and resulted in protection of the host against challenge with live *B.pertussis.*

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Jennifer Graser 4/16/02
Primary Examiner
Art Unit 1645